Case Report

Finally, She Smiled: A Case of Granulomatous Cheilitis Treated with Tofacitinib

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Abstract

Granulomatous cheilitis (GC) is a rare, idiopathic inflammatory disorder usually affecting young adults. Various treatment modalities have been suggested in the literature, but some cases remain recalcitrant and result in significant emotional distress owing to facial disfigurement. We present a 20-year-old woman with a two-year history of asymptomatic lip swelling, diagnosed as biopsy-proven GC and refractory to topical corticosteroids, tacrolimus, intralesional corticosteroids, and systemic corticosteroids. After failure of these therapies, oral tofacitinib (5 mg twice daily) for 3 months, administered with emollients, resulted in a significant improvement in swelling and disfigurement. The exact etiology of GC remains unknown, but T-helper 1-driven cytokines contribute to granuloma formation via the Janus kinase-signal transducer and activator of transcription pathway. In this refractory case, tofacitinib, a JAK1/3 inhibitor, showed promising results. While this suggests potential as a therapeutic option in recalcitrant GC, larger studies are needed to establish efficacy, safety, and the role in treatment algorithms. Known risks of JAK inhibitors, including infections, thromboembolism, cardiovascular events, and malignancy, should be considered.

Keywords: Granulomatous cheilitis, Janus kinase inhibitors, lip swelling, non-caseating granuloma, refractory cheilitis, tofacitinib

Introduction

Granulomatous cheilitis (GC), or Miescher's cheilitis, is a rare, idiopathic inflammatory condition characterized by persistent, non-tender swelling of one or both lips, predominantly affecting young adults.[1] It is considered a monosymptomatic variant of Melkersson-Rosenthal syndrome, which may include facial paralysis and fissured tongue.[2] The chronic disfigurement caused by GC often leads to significant emotional distress and reduced quality of life.[3]

The etiology of GC remains unclear, with proposed triggers including genetic predisposition, hypersensitivity reactions (e.g., to food additives or dental materials), and microbial agents like *Mycobacterium tuberculosis* or *Borrelia burgdorferi*.[4,5] Associations with systemic conditions such as Crohn's disease and sarcoidosis suggest a shared granulomatous pathology.[6] Histologically, GC is marked by non-caseating granulomas with epithelioid histiocytes, lymphocytes, and lymphoedema.[6] Immunologically, T-helper 1 (Th1) cells drive granuloma formation through cytokines like interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), which signal via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway.[7] IFN-γ activates JAK1/JAK2-STAT1, promoting macrophage polarization and granuloma maintenance, whereas TNF-α contributes via overlapping inflammatory cascades.

Clinically, GC presents with insidious lip swelling, often affecting the upper lip, which may initially be episodic but

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becomes persistent.[8] The diagnosis relies on clinical findings and biopsy to rule out mimicking conditions. A systematic review from India reported a mean onset age of 26 years, with 75% of cases being monosymptomatic.[8] Treatment is challenging due to the lack of randomized trials and variable response rates.[9] Standard therapies include topical, intralesional, or systemic corticosteroids, which often yield temporary relief.[10] Other options like antibiotics (e.g., metronidazole), immunosuppressants (e.g., thalidomide), and biologics (e.g., anti-TNF agents) have inconsistent outcomes.[11] Surgical interventions like cheiloplasty or radiofrequency therapy are reserved for severe cases but carry relapse risks.[12]

Recent evidence highlights JAK inhibitors as promising for granulomatous skin diseases by targeting the JAK-STAT pathway.[1] Tofacitinib has shown efficacy in conditions like granuloma annulare and necrobiosis lipoidica, while upadacitinib achieved high response rates in refractory GC.[4,5] This report presents a case of biopsy-proven GC successfully treated with tofacitinib after failure of conventional therapies, adding to emerging evidence on JAK inhibition in refractory granulomatous dermatoses.

Case Report

A 20-year-old female presented with a two-year history of asymptomatic swelling of both lips, with insidious onset and gradual progression, resulting in noticeable facial disfigurement. No pain, itching, or systemic symptoms (fever, weight loss, gastrointestinal complaints) were reported. No allergies, dental procedures, or family history noted.

Examination revealed diffuse, non-tender, soft-to-firm swelling of both lips, more prominent on the upper lip, without erythema, scaling, or ulceration (Figure 1a). The oral mucosa was spared; no facial palsy, fissured tongue, or lymphadenopathy was noted.

Laboratory tests [complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum angiotensin converting enzyme (ACE), antinuclear antibody, antineutrophilic cytoplasmic antibody] were normal. Patch testing was negative. Lip biopsy confirmed non-caseating granulomas with epithelioid histiocytes and lymphocytes, consistent with GC.[1]

Patient was previously treated with topical clobetasol propionate 0.05% ointment (twice daily, 4 weeks), topical tacrolimus 0.1% ointment (twice daily, 6 weeks), intralesional triamcinolone acetonide 10 mg/mL (biweekly, 3 months), systemic prednisolone 1 mg/kg/day (tapered over 8 weeks)—transient improvement were noted with recurrence and refractoriness. Systemic corticosteroids were discontinued approximately 2 months before initiation of tofacitinib.

After informed consent and baseline screening (tuberculosis Quantiferon, viral serology, and lipid profile), oral tofacitinib 5 mg twice daily and an emollient were initiated. She was counseled on risks (infections, thromboembolism, cardiovascular events, malignancy). At 1 month, partial reduction was noted (Figure 1b); at 3 months, near-complete resolution with a normal contour (Figure 1c) was achieved. dermatology life quality index improved from 18 to 4. No adverse events were noted. Tofacitinib was tapered over the next month. Remission was noted at 6-month follow-up.

Discussion

This case illustrates tofacitinib's potential in refractory GC where conventional therapies failed. The pathogenesis of GC involves Th1-mediated granuloma formation via IFN-γ and TNF-α signaling through the JAK-STAT pathway.[7,13] JAK inhibition disrupts this process and may be to broad corticosteroids by targeting specific cytokine signaling rather than causing non-selective immunosuppression, thereby reducing the risk of relapse in cytokine-driven granulomatous inflammation.

Conventional treatments yield inconsistent results much of the time. Intralesional corticosteroids are usually the first-line agents, but relapses are common.[2,8] Metronidazole is also effective in some cases.[10] Even thalidomide has shown efficacy but its use is limited by neurological adverse effects.[11] Radiofrequency therapy has also been tried in some cases.[12]

JAK inhibitors target multiple cytokines in granulomatous conditions. Tofacitinib induced remission in necrobiosis lipoidica and granuloma annulare has been reported.[4,8] Also there are case reports showing upadacitinib achieved 80% complete response in refractory GC, including Crohn's-associated.[4] Our patient's rapid response aligns with the hypothesis that JAK inhibition targets core inflammation.

Differential diagnosis includes orofacial Crohn's disease, sarcoidosis, foreign body granulomas, infectious granulomatous diseases (tuberculosis, deep fungal infections).[13] But normal serum ACE and no systemic symptoms argued against sarcoidosis; no gastrointestinal symptoms and normal labs also excluded Crohn's disease. Even the biopsy lacked caseation or organisms. The negative Quantiferon test and no travel/endemic exposure ruled out tuberculosis and negative special stains excluded fungal etiology.[14] There was no history of injection of foreign material.

Tofacitinib at low doses generally favorable, but JAK inhibitors carry risks like serious infections, thromboembolism, cardiovascular events (e.g., MACE), malignancy (Food and Drug Administration boxed warnings based on ORAL

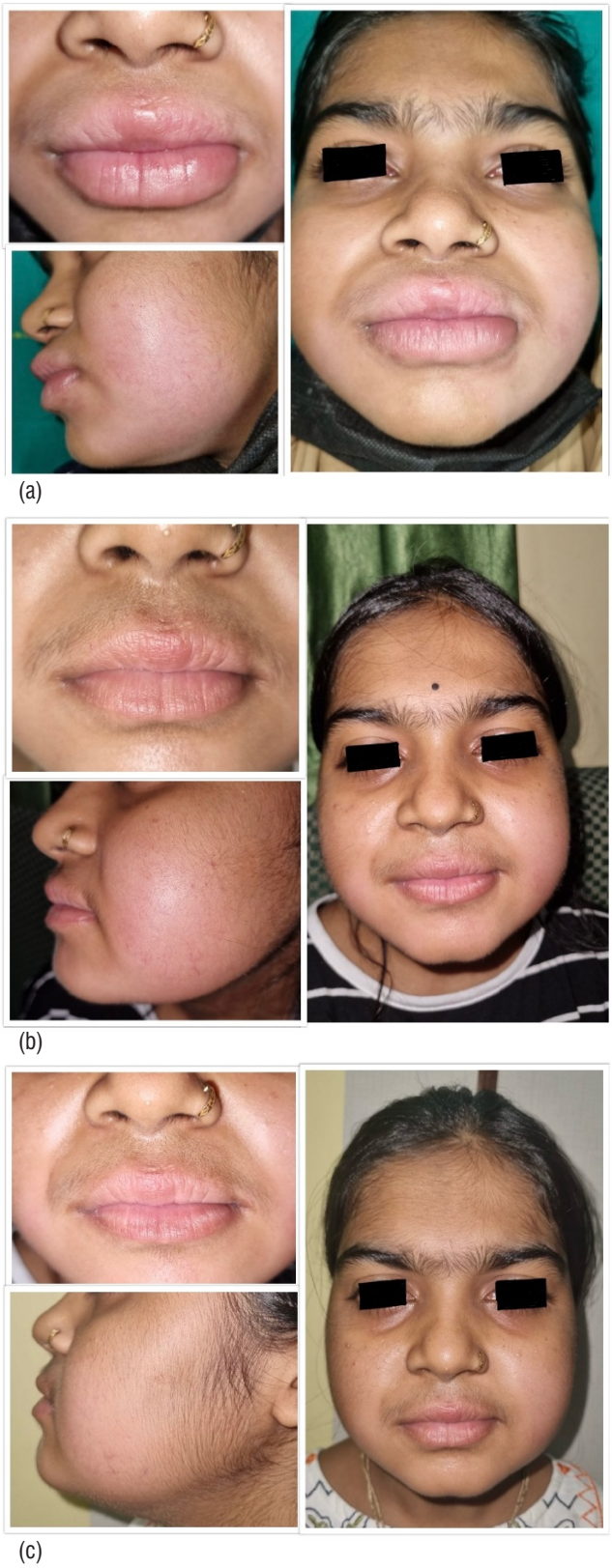

Figure 1. (a) Diffuse, non-tender, soft-to-firm swelling over both lips. (b) Partial reduction in swelling at 1 month after starting tofacitinib. (c) Near-complete resolution of lip swelling with restoration of normal lip contour at 3 months after starting tofacitinib

Surveillance trial in rheumatoid arthritis, extrapolated class-wide).[15] So, it should be used with caution in at-risk patients. In our case, it was low-dose, short-term use. No adverse events were noted.

Our case adds to limited reports of tofacitinib in GC (mostly upadacitinib data), demonstrates efficacy post-multiple failures, highlights quality-of-life benefit and contributes preliminary evidence for JAK inhibitors in recalcitrant GC.

We have limitations, including a single case and a short follow-up period. Also, it cannot establish causality or superiority. Prospective trials are needed for efficacy and safety positioning against corticosteroids.[16]

Conclusion

This case suggests that tofacitinib may be effective in refractory GC, improving clinical outcomes and quality of life without observed adverse effects. However, the evidence is exploratory and derived from case reports and case series. Larger controlled studies are required to confirm efficacy, long-term safety, and potential role as a first-line or alternative therapy, while balancing benefits against known JAK inhibitor risks.

Footnotes

Informed Consent: Patient consent for publication of images obtained.

Authorship Contributions

Concept: S.P., Design: S.M., Literature Search: S.P., Writing: S.M.

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